General

Guideline Title

Neutropenic sepsis: prevention and management of neutropenic sepsis in cancer patients.

Bibliographic Source(s)

National Collaborating Centre for Cancer. Neutropenic sepsis: prevention and management of neutropenic sepsis in cancer patients. London (UK): National Institute for Health and Clinical Excellence (NICE); 2012 Sep. 31 p. (Clinical guideline; no. 151).

Guideline Status

This is the current release of the guideline.

Regulatory Alert

FDA Warning/Regulatory Alert

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- May 12, 2016 – Fluoroquinolone Antibacterial Drugs : The U.S. Food and Drug Administration (FDA) is advising that the serious side effects associated with fluoroquinolone antibacterial drugs generally outweigh the benefits for patients with sinusitis, bronchitis, and uncomplicated urinary tract infections who have other treatment options. For patients with these conditions, fluoroquinolones should be reserved for those who do not have alternative treatment options.

Recommendations

Major Recommendations

Note from the National Guideline Clearinghouse (NGC): This guideline was developed by the National Collaborating Centre for Cancer (NCC-C) on behalf of the National Institute for Health and Clinical Excellence (NICE) (see the "Availability of Companion Documents" field for the full version of this guidance).

Information, Support and Training

Information and Support for Patients and Carers

Provide patients having anticancer treatment and their carers with written and oral information, both before starting and throughout their anticancer treatment, on:

- Neutropenic sepsis
- How and when to contact 24-hour specialist oncology advice
- How and when to seek emergency care

Training for Healthcare Professionals

Healthcare professionals and staff who come into contact with patients having anticancer treatment should be provided with training on neutropenic sepsis. The training should be tailored according to the type of contact.

Reducing the Risk of Septic Complications of Anticancer Treatment

For adult patients (aged 18 years and older) with acute leukaemias, stem cell transplants or solid tumours in whom significant neutropenia (neutrophil count 0.5×10^9 per litre or lower) is an anticipated consequence of chemotherapy, offer prophylaxis with a fluoroquinolone during the expected period of neutropenia only.

Rates of antibiotic resistance and infection patterns should be monitored in treatment facilities where patients are having fluoroquinolones for the prophylaxis of neutropenic sepsis.*

Do not routinely offer granulocyte colony-stimulating factor (G-CSF) for the prevention of neutropenic sepsis in adults receiving chemotherapy unless they are receiving G-CSF as an integral part of the chemotherapy regimen or in order to maintain dose intensity.

*For more information see the Department of Health's Updated guidance on the diagnosis and reporting of Clostridium difficile and guidance from the Health Protection Agency and the Department of Health on Clostridium difficile infection: how to deal with the problem.

When to Refer Patients in the Community for Suspected Neutropenic Sepsis

Suspect neutropenic sepsis in patients having anticancer treatment who become unwell.

Refer patients with suspected neutropenic sepsis immediately for assessment in secondary or tertiary care.

Managing Suspected Neutropenic Sepsis in Secondary and Tertiary Care

Emergency Treatment and Assessment

Treat suspected neutropenic sepsis as an acute medical emergency and offer empiric antibiotic therapy immediately.

Include in the initial clinical assessment of patients with suspected neutropenic sepsis:

- History and examination
- Full blood count, kidney and liver function tests (including albumin), C-reactive protein, lactate and blood culture

Further Assessment

After completing the initial clinical assessment try to identify the underlying cause of the sepsis by carrying out:

- Additional peripheral blood culture in patients with a central venous access device if clinically feasible
- Urinalysis in all children aged under 5 years

Do not perform a chest X-ray unless clinically indicated.

Starting Antibiotic Therapy

All Patients

Offer beta lactam monotherapy with piperacillin with tazobactam* as initial empiric antibiotic therapy to patients with suspected neutropenic sepsis who need intravenous treatment unless there are patient-specific or local microbiological contraindications.

Do not offer an aminoglycoside, either as monotherapy or in dual therapy, for the initial empiric treatment of suspected neutropenic sepsis unless there are patient-specific or local microbiological indications.

*At the time of publication (September 2012) piperacillin with tazobactam did not have a United Kingdom (UK) marketing authorisation for use in children aged under 2 years. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The child's parent or carer should provide informed consent, which should be documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors and the prescribing advice provided by the Joint Standing Committee on Medicines (a joint committee of the Royal College of Paediatrics and Child Health and the Neonatal and Paediatric Pharmacists Group) for further information.

Empiric Glycopeptide Antibiotics in Patients with Central Venous Access Devices

Do not offer empiric glycopeptide antibiotics to patients with suspected neutropenic sepsis who have central venous access devices unless there are patient-specific or local microbiological indications.

Do not remove central venous access devices as part of the initial empiric management of suspected neutropenic sepsis.

Confirming a Diagnosis of Neutropenic Sepsis

Diagnose neutropenic sepsis in patients having anticancer treatment whose neutrophil count is 0.5×10^9 per litre or lower and who have either:

- A temperature higher than 38ºC or
- Other signs or symptoms consistent with clinically significant sepsis

Managing Confirmed Neutropenic Sepsis

Assessing the Patient's Risk of Septic Complications

A healthcare professional with competence in managing complications of anticancer treatment should assess the patient's risk of septic complications within 24 hours of presentation to secondary or tertiary care, basing the risk assessment on presentation features and using a validated risk scoring system*.

*Examples of risk scoring systems include The Multinational Association for Supportive Care in Cancer risk index: a multinational scoring system for identifying low-risk febrile neutropenic cancer patients (Journal of Clinical Oncology 2000; 18: 3038–51) and the modified Alexander rule for children (aged under 18) (European Journal of Cancer 2009; 45: 2843–9).

Patients at Low Risk of Septic Complications

Consider outpatient antibiotic therapy for patients with confirmed neutropenic sepsis and a low risk of developing septic complications, taking into account the patient's social and clinical circumstances and discussing with them the need to return to hospital promptly if a problem develops.

Patients at High Risk of Septic Complications

For patients with confirmed neutropenic sepsis and a high risk of developing septic complications, a healthcare professional with competence in managing complications of anticancer treatment should daily:

- Review the patient's clinical status
- Reassess the patient's risk of septic complications, using a validated risk scoring system*

Do not switch initial empiric antibiotics in patients with unresponsive fever unless there is clinical deterioration or a microbiological indication.

Switch from intravenous to oral antibiotic therapy after 48 hours of treatment in patients whose risk of developing septic complications has been reassessed as low by a healthcare professional with competence in managing complications of anticancer treatment using a validated risk scoring system*.

Offer discharge to patients having empiric antibiotic therapy for neutropenic sepsis only after:

- The patient's risk of developing septic complications has been reassessed as low by a healthcare professional with competence in managing complications of anticancer treatment using a validated risk scoring system* and
- Taking into account the patient's social and clinical circumstances and discussing with them the need to return to hospital promptly if a problem develops

*Examples of risk scoring systems include The Multinational Association for Supportive Care in Cancer risk index: a multinational scoring system

for identifying low-risk febrile neutropenic cancer patients (Journal of Clinical Oncology 2000; 18: 3038–51) and the modified Alexander rule for children (aged under 18) (European Journal of Cancer 2009; 45: 2843–9).

Duration of Empiric Antibiotic Treatment

Continue inpatient empiric antibiotic therapy in all patients who have unresponsive fever unless an alternative cause of fever is likely.

Discontinue empiric antibiotic therapy in patients whose neutropenic sepsis has responded to treatment, irrespective of neutrophil count.

Clinical Algorithm(s)

The recommendations from this guideline have been incorporated into a NICE pathway.

Conventional algorithms of the summary of recommendations and for an overview of high and low risk management are also found in the full guideline document (see the "Availability of Companion Documents" field).

Scope

Disease/Condition(s)

Neutropenic sepsis related to anticancer treatment

Guideline Category

Counseling

Diagnosis

Evaluation

Management

Risk Assessment

Treatment

Clinical Specialty

Critical Care

Emergency Medicine

Family Practice

Hematology

Internal Medicine

Nursing

Oncology

Pediatrics

Preventive Medicine

Intended Users

Advanced Practice Nurses

Health Care Providers

Hospitals

Nurses

Patients

Pharmacists

Physician Assistants

Physicians

Guideline Objective(s)

- To improve outcomes by providing evidence-based recommendations on the prevention, identification and management of neutropenic sepsis, a life-threatening complication of cancer treatment
- To address key clinical issues listed in areas that were known to be controversial or uncertain, where there was identifiable practice variation, or where National Institute for Health and Clinical Excellence (NICE) guidelines were likely to have most impact

Target Population

Children, young people and adults in the United Kingdom with cancer (haematological and solid tumour malignancies) receiving anticancer treatment in National Health Service (NHS) settings

Note: This guideline does not address children, young people and adults with neutropenia or neutropenic sepsis not caused by anticancer treatment.

Interventions and Practices Considered

Counseling/Prevention

1. Written and oral information for patients and carers
2. Training for health care professionals
3. Fluoroquinolone prophylaxis during neutropenic episodes
4. Monitoring of antibiotic resistance rates and infection patterns in treatment facilities
5. Maintaining high level of suspicion of neutropenic sepsis if patient is unwell
6. Immediate referral to secondary or tertiary care if patient is unwell

Treatment/Management

1. Treat suspected case of neutropenic sepsis as an acute emergency
2. Obtain history, examination, full blood count, kidney and liver function tests (including albumin), C-reactive protein, lactate and blood culture
3. Additional peripheral blood cultures in patients with a central venous access device if clinically feasible
4. Urinalysis in all children aged under 5 years
5. Chest x-ray only if clinically indicated
6. Start initial empiric antibiotic therapy
    - β-lactam monotherapy with piperacillin and tazobactam (see note in the "Major Recommendations" field)
    - Retain central venous catheter
7. Confirm diagnosis of neutropenic sepsis based on blood count and either body temperature or other symptoms
8. Assess risk of septic complications within 24 hours in patients with confirmed neutropenic sepsis
    - Consider outpatient antibiotics if risk is low

    - Daily review of patient status and reassessment of risk if risk is high
9. Maintain empiric antibiotics unless there is clinical deterioration or a microbiological indication for change
10. Switch from intravenous to oral antibiotics once risk of complications is low
11. Discharge patient with low risk of septic complications if social and clinical situation permit
12. Continue inpatient empiric antibiotic therapy for unresponsive fever unless an alternative cause of fever is likely
13. Discontinue empiric antibiotic therapy if neutropenic sepsis has responded to treatment

Note: The following were considered and not recommended:

Granulocyte colony-stimulating factor prophylaxis (unless part of the chemotherapy regimen)
Initial empiric antibiotic therapy with aminoglycoside monotherapy or combination therapy unless there are patient-specific or local microbiological indications
Initial empiric antibiotic therapy with glycopeptide in patients with a central venous catheter unless there are patient-specific or local microbiological indications

Major Outcomes Considered

- Mortality from neutropenic sepsis
- Morbidity (for example renal impairment)
- Hospitalisation rates
- Length of hospital stay
- Recurrence rate
- Time to treatment of neutropenic sepsis
- Health-related quality of life assessments (or surrogates, such as 'acceptability' or 'preference')
- Cost effectiveness of treatment

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Note from the National Guideline Clearinghouse (NGC): This guideline was developed by the National Collaborating Centre for Cancer (NCC-C) on behalf of the National Institute for Health and Clinical Excellence (NICE) (see the "Availability of Companion Documents" field for the full version of this guidance).

Review of Clinical Literature

Scoping Search

An initial scoping search for published guidelines, systematic reviews, economic evaluations and ongoing research was carried out on the following databases or websites: National Library for Health (NLH) Guidelines Finder (now NHS Evidence), National Guidelines Clearinghouse, Cochrane Database of Systematic Reviews (CDSR), Heath Technology Assessment Database (HTA), NHS Economic Evaluations Database (NHSEED), DH Data, Medline and Embase.

At the beginning of the development phase, initial scoping searches were carried out to identify any relevant guidelines (local, national or international) produced by other groups or institutions.

Searching For the Evidence

In order to answer each question the NCC-C information specialist developed a search strategy to identify relevant published evidence for both clinical and cost effectiveness. Key words and terms for the search were agreed in collaboration with the GDG. When required, the health economist searched for supplementary papers to inform detailed health economic work (see section on "Incorporating Health Economic Evidence" below).

Search filters, such as those to identify systematic reviews (SRs) and randomised controlled trials (RCTs) were applied to the search strategies when there was a wealth of these types of studies. No language restrictions were applied to the search; however, foreign language papers were not requested or reviewed (unless of particular importance to that question).

The following databases were included in the literature search:

- The Cochrane Library Medline and Premedline 1950 onwards
- Excerpta Medica (Embase) 1980 onwards
- Cumulative Index to Nursing and Allied Health Literature (Cinahl) 1982 onwards
- Allied & Complementary Medicine (AMED) 1985 onwards
- British Nursing Index (BNI) 1985 onwards
- Psychinfo 1806 onwards
- Web of Science (specifically Science Citation Index Expanded [SCI-EXPANDED] 1899 onwards and Social Sciences Citation Index [SSCI] 1956 onwards)
- Biomed Central 1997 onwards

From this list the information specialist sifted and removed any irrelevant material based on the title or abstract before passing to the researcher. All the remaining articles were then stored in a Reference Manager electronic library.

Searches were updated and re-run 8–10 weeks before the stakeholder consultation, thereby ensuring that the latest relevant published evidence was included in the database. Any evidence published after this date was not included. For the purposes of updating this guideline, November 2011 should be considered the starting point for searching for new evidence.

Further details of the search strategies, including the methodological filters used, are provided in the evidence review in the full guideline document.

Critical Appraisal

From the literature search results database, one researcher scanned the titles and abstracts of every article for each question and full publications were ordered for any studies considered relevant or if there was insufficient information from the title and abstract to inform a decision. When the papers were obtained the researcher applied inclusion/exclusion criteria to select appropriate studies, which were then critically appraised. For each question, data on the type of population, intervention, comparator and outcomes (PICO) were extracted and recorded in evidence tables and an accompanying evidence summary prepared for the GDG (see evidence review in full guideline document). All evidence was considered carefully by the GDG for accuracy and completeness.

Incorporating Health Economics Evidence

Prioritising Topics for Economic Analysis

After the clinical questions had been defined, and with the help of the health economist, the GDG discussed and agreed which of the clinical questions were potential priorities for economic analysis. These economic priorities were chosen on the basis of the following criteria, in broad accordance with the NICE guidelines manual (see the "Availability of Companion Documents" field):

- The overall importance of the recommendation, which may be a function of the number of patients affected and the potential impact on costs and health outcomes per patient
- The current extent of uncertainty over cost effectiveness, and the likelihood that economic analysis will reduce this uncertainty
- The feasibility of building an economic model

For each topic, a review of the economic literature was conducted. Where published economic evaluation studies were identified that addressed the economic issues for a clinical question, these are presented alongside the clinical evidence wherever possible. For those clinical areas reviewed, the information specialists used a similar search strategy as used for the review of clinical evidence but with the inclusion of a health economics filter.

For systematic searches of published economic evidence, the following databases were included:

- Medline
- Embase
- NHS Economic Evaluation Database (NHS EED)
- Health Technology Assessment (HTA)
- Health Economic Evaluations Database (HEED)

Methods for Reviewing and Appraising Economic Evidence

The aim of reviewing and appraising the existing economic literature is to identify relevant economic evaluations that compare both costs and health consequences of alternative interventions and that are applicable to NHS practice. Thus studies that only report costs, non-comparative studies or 'cost of illness' studies are generally excluded from the reviews.

Economic studies identified through a systematic search of the literature are appraised using a methodology checklist designed for economic evaluations (NICE guideline manual, Appendix H [see the "Availability of Companion Documents" field). This checklist is not intended to judge the quality of a study per se, but to determine whether an existing economic evaluation is useful to inform the decision-making of the GDG for a specific topic within the Guideline. There are two parts to the appraisal process; the first step is to assess applicability (i.e., the relevance of the study to the specific guideline topic and the NICE reference case) (see Table D in the full guideline document). In the second step, only those studies deemed directly or partially applicable are further assessed for limitations (i.e., the methodological quality, see Table E in the full guideline document).

Number of Source Documents

Cost-effectiveness evidence for primary and secondary prophylaxis with colony-stimulating factors (CSFs) = 10

See the full evidence review (see the "Availability of Companion Documents" field) for the numbers of source documents for each topic.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Overall Quality of Outcome Evidence in GRADE (Grading of Recommendations Assessment, Development and Evaluation)

Level	Description
High	Further research is very unlikely to change confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate
Very Low	Any estimate of effect is very uncertain

Methods Used to Analyze the Evidence

Meta-Analysis

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Note from the National Guideline Clearinghouse (NGC): This guideline was developed by the National Collaborating Centre for Cancer (NCC-C) on behalf of the National Institute for Health and Clinical Excellence (NICE) (see the "Availability of Companion Documents" field for the full version of this guidance).

Developing the Review Protocol

For each clinical question, the information specialist and researcher (with input from other technical team and Guideline Development Group [GDG] members) prepared a review protocol. This protocol explained how the review was to be carried out in order to develop a plan of how to review the evidence, limit the introduction of bias and for the purposes of reproducibility. All review protocols can be found in the full evidence review (see the "Availability of Companion Documents" field).

GRADE (Grading of Recommendations, Assessment, Development and Evaluation)

For interventional questions, studies which matched the inclusion criteria were evaluated and presented using a modification of GRADE (NICE 2009; http://www.gradeworkinggroup.org/). Where possible this included meta-analysis and synthesis of data into a GRADE 'evidence profile'. The evidence profile shows, for each outcome, an overall assessment of both the quality of the evidence as a whole (low, moderate or high) as well as an estimate of the size of effect. A narrative summary (evidence statement) was also prepared.

Each topic outcome was examined for the quality elements defined in Table B in the full guideline document (see the "Availability of Companion Documents" field) and subsequently graded using the quality levels listed in the "Rating Scheme for the Strength of the Evidence" field. The reasons for downgrading or upgrading specific outcomes were explained in footnotes.

All procedures were fully compliant with NICE methodology as detailed in the 'NICE guidelines manual' (see the "Availability of Companion Documents" field). In general, no formal contact was made with authors; however, there were ad hoc occasions when this was required in order to clarify specific details.

For non-interventional questions, for example the questions regarding diagnostic test accuracy, a narrative summary of the quality of the evidence was given.

Methods for Reviewing and Appraising Economic Evidence

Where relevant, a summary of the main findings from the systematic search, review and appraisal of economic evidence is presented in an economic evidence profile alongside the GRADE table for clinical evidence (see the "Rating Scheme for the Strength of the Evidence" field).

If high-quality published economic evidence relevant to current NHS practice was identified through the search, the existing literature was reviewed and appraised. However, it is often the case that published economic studies may not be directly relevant to the specific clinical question as defined in the guideline or may not be comprehensive or conclusive enough to inform UK practice. In such cases, for priority topics, consideration was given to undertaking a new economic analysis as part of this guideline.

Economic Modelling

Once the need for a new economic analysis for high priority topics had been agreed by the GDG, the health economist investigated the feasibility of developing an economic model. In the development of the analysis, the following general principles were adhered to:

- The GDG subgroup was consulted during the construction and interpretation of the analysis
- The analysis was based on the best available clinical evidence from the systematic review
- Assumptions were reported fully and transparently
- Uncertainty was explored through sensitivity analysis
- Costs were calculated from a health services perspective
- Outcomes were reported in terms of quality-adjusted life years

Methods Used to Formulate the Recommendations

Expert Consensus

Informal Consensus

Description of Methods Used to Formulate the Recommendations

Note from the National Guideline Clearinghouse (NGC): This guideline was developed by the National Collaborating Centre for Cancer (NCC-C) on behalf of the National Institute for Health and Clinical Excellence (NICE) (see the "Availability of Companion Documents" field for the full version of this guidance).

Overview

The development of the guideline was based upon methods outlined in the NICE guidelines manual (see the "Availability of Companion Documents" field). A team of health professionals, lay representatives and technical experts known as the Guideline Development Group (GDG), with support from the NCC-C staff, undertook the development of this clinical guideline. The basic steps in the process of developing a guideline are listed and discussed below:

- Using the remit, define the scope which sets the inclusion/exclusion criteria of the guideline
- Forming the GDG
- Developing clinical questions
- Identifying the health economic priorities
- Developing the review protocol
- Systematically searching for the evidence
- Appraising the evidence
- Incorporating health economic evidence
- Distilling and synthesising the evidence writing recommendations
- Agreeing the recommendations
- Structuring and writing the guideline
- Updating the guideline

The Guideline Development Group (GDG)

The neutropenic sepsis GDG was recruited in line with the NICE guidelines manual (see the "Availability of Companion Documents" field). The first step was to appoint a Chair and a Lead Clinician. Advertisements were placed for both posts and candidates were interviewed before being offered the role. The NCC-C Director, GDG Chair and Lead Clinician identified a list of specialties that needed to be represented on the GDG. Details of the adverts were sent to the main stakeholder organisations, cancer networks and patient organisations/charities. Individual GDG members were selected by the NCC-C Director, GDG Chair and Lead Clinician, based on their application forms. The guideline development process was supported by staff from the NCC-C, who undertook the clinical and health economics literature searches, reviewed and presented the evidence to the GDG, managed the process and contributed to drafting the guideline.

Guideline Development Group Meetings

Eleven GDG meetings were held between September 21, 2010 and May 18, 2012. During each GDG meeting (held over either one or two days) clinical questions and clinical and economic evidence were reviewed, assessed and recommendations formulated. At each meeting patient/carer and service-user concerns were routinely discussed as part of a standing agenda item.

NCC-C project managers divided the GDG workload by allocating specific clinical questions, relevant to their area of clinical practice, to small sub-groups of the GDG in order to simplify and speed up the guideline development process. These groups considered the evidence, as reviewed by the researcher, and synthesised it into draft recommendations before presenting it to the GDG as a whole. Each clinical question was led by a GDG member with expert knowledge of the clinical area (usually one of the healthcare professionals). The GDG subgroups often helped refine the clinical questions and the clinical definitions of treatments. They also assisted the NCC-C team in drafting the section of the guideline relevant to their specific topic.

Patient/Carer Members

Individuals with direct experience of neutropenic sepsis gave an important user focus to the GDG and the guideline development process. The GDG included three patient/carer members. They contributed as full GDG members to writing the clinical questions, helping to ensure that the evidence addressed their views and preferences, highlighting sensitive issues and terminology relevant to the guideline and bringing service-user research to the attention of the GDG.

Needs Assessment

As part of the guideline development process the NCC-C invited a specialist registrar, with the support of the GDG, to undertake a needs

assessment. The needs assessment aims to describe the burden of disease and current service provision for patients with neutropenic sepsis in England and Wales, which informed the development of the guideline.

Assessment of the effectiveness of interventions is not included in the needs assessment, and was undertaken separately by researchers in the NCC-C as part of the guideline development process. The information included in the needs assessment document was presented to the GDG. Most of the information was presented in the early stages of guideline development, and other information was included to meet the evolving information needs of the GDG during the course of guideline development.

Agreeing to the Recommendations

For each clinical question the GDG were presented with a summary of the clinical evidence, and, where appropriate, economic evidence, derived from the studies reviewed and appraised. From this information the GDG were able to derive the guideline recommendations. The link between the evidence and the view of the GDG in making each recommendation is made explicit in the accompanying Linking Evidence to Recommendations (LETR) statement.

LETR (Linking Evidence to Recommendations) Statements

As clinical guidelines were previously formatted, there was limited scope for expressing how and why a GDG made a particular recommendation from the evidence of clinical and cost effectiveness. To make this process more transparent to the reader, NICE have introduced an explicit, easily understood and consistent way of expressing the reasons for making each recommendation. This is known as the 'LETR statement' and will usually cover the following key points:

- The relative value placed on the outcomes considered
- The strength of evidence about benefits and harms for the intervention being considered
- The costs and cost-effectiveness of an intervention
- The quality of the evidence (see the GRADE [Guideline Recommendations Assessment, Development and Evaluation] in the full guideline document and the "Rating Scheme for the Strength of the Evidence" field)
- The degree of consensus within the GDG
- Other considerations – for example equalities issues.

Where evidence was weak or lacking the GDG agreed to the final recommendations through informal consensus. Shortly before the consultation period, ten key priorities and five key research recommendations were selected by the GDG for implementation and the patient algorithms were agreed to. To avoid giving the impression that higher grade recommendations are of higher priority for implementation, NICE no longer assigns grades to recommendations.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A cost-utility analysis of primary and secondary prophylaxis with granulocyte (macrophage) colony stimulating factor G(M)-CSF and/or quinolones for the prevention of neutropenic sepsis was undertaken.

Analysis

Aim

The aim of this economic analysis was to examine which of the following prophylactic strategies is the most cost-effective for cancer patients who are receiving outpatient chemotherapy (defined as patients with planned inpatient treatment of less than 10-days post- chemotherapy):

- Nothing/placebo
- Primary prophylaxis with quinolones
- Primary prophylaxis with G-CSF
- Primary prophylaxis with G-CSF and quinolones
- Primary prophylaxis with pegylated (PEG) G-CSF
- Secondary prophylaxis with quinolones

- Secondary prophylaxis with G-CSF
- Secondary prophylaxis with G-CSF and quinolones
- Secondary prophylaxis with PEG-G-CSF

A subgroup analysis was conducted for the following three patient groups:

- Patients with a solid tumour (aged 18 years and older)
- Patients with non-Hodgkin lymphoma (aged 18 years and older)
- Patients with Hodgkin lymphoma (aged 18 years and older)

Key Model Assumptions

- None of the prophylaxis strategies included in the model could improve patient's short-term mortality.
- The sensitivity and specificity of diagnosing neutropenic sepsis is 100%.
- Patients could only develop one episode of neutropenic sepsis during one cycle of chemotherapy.
- If a patient stops receiving chemotherapy, he or she would not be at risk of developing neutropenic sepsis.
- The effectiveness of each prophylactic strategy (relative reduction of neutropenic sepsis) would be the same for patients at different levels of risk of developing neutropenic sepsis.
- The effectiveness of each prophylactic strategy (relative reduction of neutropenic sepsis) would be the same for patients who are receiving primary or secondary prophylaxis.

Summary of Results

The aim of this economic analysis was to determine which prophylactic strategy is the most cost-effective for cancer patients who are receiving chemotherapy.

The findings of the base-case analysis for all three patient sub–groups are summarised below.

At the National Institute for Health and Clinical Excellence (NICE) willingness to pay (WTP) threshold of £20,000 per quality-adjusted life year (QALY):

- For patients with a solid tumour and who can take quinolone, primary prophylaxis with quinolone is the most cost-effective prophylactic strategy
- For patients with a solid tumour and who cannot take quinolone, no prophylaxis is the most cost-effective strategy
- For patients with non-Hodgkin lymphoma or Hodgkin lymphoma, no prophylaxis is the most cost-effective strategy

All the results in the analysis were robust to both structural sensitivity analysis and probabilistic sensitivity analysis.

The one-way sensitivity analysis that was conducted showed that the model was robust to all scenarios tested (Section A4.2 of the full guideline document), except for relative risk of neutropenic sepsis (quinolone versus nothing/placebo) and discounting the cost of pegylated (PEG) G-CSF.

For patients with a solid tumour and who can take quinolone:

- When the relative risk of a neutropenic sepsis episode (quinolones versus nothing/placebo) was above 0.787, nothing/placebo became the most cost-effective strategy, at a WTP threshold of £20,000 per QALY

For patients with a solid tumour and who cannot take quinolone:

- When the discount to the cost of PEG-G-CSF was over 73.85% (corresponding price: £179.5 per single subcutaneous injection [6 mg]), secondary prophylaxis with PEG-G-CSF became the most cost-effective strategy
- When the discount to the cost of PEG-G-CSF was over 84.13% (corresponding price: £108.9 per single subcutaneous injection [6 mg]), primary prophylaxis with PEG-G-CSF became the most cost-effective strategy.

For patients with non-Hodgkin lymphoma:

- When the discount to the cost of PEG-G-CSF was over 83.49% (corresponding price: £113.3 per single subcutaneous injection [6 mg]), secondary prophylaxis with PEG-G-CSF became the most cost-effective strategy
- When the discount to the cost of PEG-G-CSF was over 89.12% (corresponding price: £74.7 per single subcutaneous injection [6 mg]), primary prophylaxis with PEG-G-CSF became the most cost-effective strategy

Primary or secondary prophylaxis with G(M)-CSF is never the most cost-effective strategy for any of the three patient groups of interest, even when extreme scenarios were considered, for example: 100% risk of neutropenic sepsis per cycle of chemotherapy, 90% drug discount of G(M)-CSF, reduced days of using G(M)-CSF (5-day per cycle of chemotherapy), reduced daily dose (one vial of G[M]-CSF for all adult patients regardless of weight) etc.

Full details of the analysis, discussion, and limitations are available in the full guideline document (see the "Availability of Companion Documents" field).

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

The guideline was validated through two consultations.

1. The first draft of the guideline (the full guideline, National Institute for Health and Clinical Excellence [NICE] guideline, and Quick Reference Guide) were consulted with Stakeholders and comments were considered by the Guideline Development Group (GDG)
2. The final consultation draft of the Full guideline, the NICE guideline and the Information for the Public were submitted to stakeholders for final comments.

The final draft was submitted to the Guideline Review Panel for review prior to publication.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Improvement in the care of patients having treatment for cancer who are at risk of neutropenic sepsis

Potential Harms

- Kidney damage and hearing impairment from aminoglycosides, e.g., gentamicin and tobramicin
- Bone pain, headache, nausea, and local injection reactions from granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony stimulating factor (GM-CSF)
- Antimicrobial resistance, e.g., Enterobacteriaceae resistance to fluoroquinolone, *Clostridium difficile* selection with fluoroquinolone

Contraindications

Contraindications

There may be patient-specific or microbiological contraindications to specific therapies.

Qualifying Statements

Qualifying Statements

- This guidance represents the view of National Institute for Health and Clinical Excellence (NICE), which was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer, and informed by the summary of product characteristics of any drugs they are considering.
- Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to avoid unlawful discrimination and to have regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.
- The Guideline Development Group (GDG) assumes that healthcare professionals will use clinical judgment, knowledge and expertise when deciding whether it is appropriate to apply these guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here must be made by the practitioner in light of individual patient circumstances, the wishes of the patient and clinical expertise.
- Treatment and care should take into account patients' needs and preferences. Patients should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals. If patients do not have the capacity to make decisions, healthcare professionals should follow the Department of Health's advice on consent and the code of practice that accompanies the Mental Capacity Act. In Wales, healthcare professionals should follow advice on consent from the Welsh Government.
- If the person is under 16, healthcare professionals should follow the guidelines in Seeking consent: working with children .

Implementation of the Guideline

Description of Implementation Strategy

The National Institute for Health and Clinical Excellence (NICE) has developed tools to help organisations implement this guidance. These are available on the NICE Web site (http://guidance.nice.org.uk/CG151 ; see also the "Availability of Companion Documents" field).

Implementation Tools

Audit Criteria/Indicators

Chart Documentation/Checklists/Forms

Clinical Algorithm

Patient Resources

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

National Collaborating Centre for Cancer. Neutropenic sepsis: prevention and management of neutropenic sepsis in cancer patients. London (UK): National Institute for Health and Clinical Excellence (NICE); 2012 Sep. 31 p. (Clinical guideline; no. 151).

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2012 Sep

Guideline Developer(s)

National Collaborating Centre for Cancer - National Government Agency [Non-U.S.]

Source(s) of Funding

National Institute for Health and Clinical Excellence (NICE)

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Guideline Committee

Guideline Development Group (GDG)

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Financial Disclosures/Conflicts of Interest

At the start of the guideline development process all Guideline Development Group (GDG) members' interests were recorded on a standard declaration form that covered consultancies, fee-paid work, share-holdings, fellowships and support from the healthcare industry. At all subsequent GDG meetings, members declared new, arising conflicts of interest which were always recorded.

The interests that were declared are provided in Appendix E.1 of the full guideline document (see the "Availability of Companion Documents" field).

Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available from the National Institute for Health and Clinical Excellence (NICE) Web site .

Availability of Companion Documents

The following are available:

- Neutropenic sepsis: prevention and management of neutropenic sepsis in cancer patients. Full guideline. London (UK): National Institute for Clinical Excellence (NICE); 2012 Sep. 262 p. (Clinical guideline; no. 151). Electronic copies: Available in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site .
- Neutropenic sepsis: prevention and management of neutropenic sepsis in cancer patients. Full evidence review. London (UK): National Institute for Clinical Excellence (NICE); 2012 Sep. 584 p. (Clinical guideline; no. 151). Electronic copies: Available in Portable Document Format (PDF) from the NICE Web site .
- Neutropenic sepsis. Baseline assessment tool. London (UK): National Institute for Clinical Excellence (NICE); 2012 Sep. (Clinical guideline; no. 151). Electronic copies: Available from NICE Web site .
- Neutropenic sepsis. Clinical audit tools. London (UK): National Institute for Clinical Excellence (NICE); 2012 Sep. (Clinical guideline; no. 151). Electronic copies: Available from NICE Web site .
- Neutropenic sepsis. Costing report. London (UK): National Institute for Clinical Excellence (NICE); 2012 Sep. (Clinical guideline; no. 151). Electronic copies: Available in Portable Document Format (PDF) from NICE Web site .
- Neutropenic sepsis. Costing template. London (UK): National Institute for Clinical Excellence (NICE); 2012 Sep. (Clinical guideline; no. 151). Electronic copies: Available from NICE Web site .
- Neutropenic sepsis: Prophylaxis podcast with Dr Bob Phillips. Podcast. London (UK): National Institute for Clinical Excellence (NICE); 2012 Sep. (Clinical guideline; no. 151). Available from NICE Web site .
- NICE Pathways. Neutropenic sepsis: Overview. London (UK): National Institute for Clinical Excellence (NICE); 2012 Jun. Electronic copies: Available from the NICE Web site .
- The guidelines manual 2009. London (UK): National Institute for Health and Clinical Excellence (NICE); 2009 Jan. Electronic copies: Available from the NICE Archive Web site .

Patient Resources

The following is available:

- Neutropenic sepsis in people having anticancer treatment. Understanding NICE guidance. London: National Institute for Health and Clinical Excellence (NICE); 2012 Sep. 11 p. Electronic copies: Available in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

This summary was completed by ECRI Institute on October 30, 2012. This summary was updated by ECRI Institute on October 25, 2013 following the U.S. Food and Drug Administration advisory on Fluoroquinolone Antibacterial Drugs. This summary was updated by ECRI Institute on May 18, 2016 following the U.S. Food and Drug Administration advisory on Fluoroquinolone Antibacterial Drugs.

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